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A Facile and Efficient Carbodiimide-Mediated Synthesis of Dihydroquinazolines via a Tandem Nucleophilic Addition-Intramolecular Hetero Conjugate Addition Annulation Strategy

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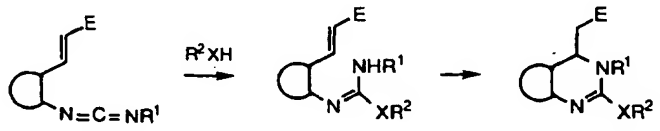
Abstract: A novel and efficient method is described for the synthesis of dihydroquinazoline derivatives which involves initial addition of a nucleophile (alcohol, amine and thiol) to the carbodiimide cumulenic system followed by intramolecular hetero conjugate addition annulation.

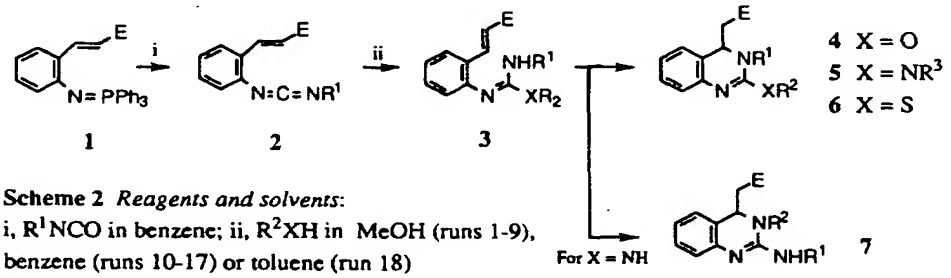
The synthetic versatility of functionalized unsaturation-conjugated heterocumulenes has increasingly become apparent because of their rich chemistry, particularly in the field of heterocyclic chemistry.[1] The so-called tandem aza-Wittig reaction-conjugated carbodiimide-mediated electrocyclization methodology has successfully developed by Molina et al.[2] and by us.[3,4] Other related tandem carbodiimide-mediated annulations, *e.g.*, intramolecular A_N and S_N, and Diels-Alder reactions, have also been widely utilized in heterocyclic synthesis.[3-5] Thus, diverse ring-forming transformations by use of a heterocumulenic system incorporating an adjacent functional group can provide facile and efficient access to a wide variety of nitrogen-containing heterocycles.[2-5] In this context we have designed carbodiimides **A** bearing a Michael acceptor in a molecule which should take part in the ring formation to give a heterocycle **C** via intramolecular conjugate addition of **B** after addition of a nucleophile to one of the cumulene double bonds in **A**. We now report how readily and efficiently the dihydroquinazoline derivatives can be obtained by this strategy.



Scheme 1 **A** **B** **C**

Carbodiimides **2** were prepared in good yields by the aza-Wittig reaction of iminophosphoranes with isocyanates.[3-5] The conversion **2** → **4a-e** was easily accomplished by simply heating **2** in methanol (Table 1, runs 1-5). The NaOMe-catalyzed reaction at room temperature was also found to be effective to afford **4e-h** in good yields. In either the catalyzed or uncatalyzed (thermal) reaction, the cyclohexyl substituent in R^1 (runs 3 and 8) required longer reaction times than the other substituents, presumably due to the steric hindrance encountered in the cyclization step of **3**. With piperidine **2** (R^1 = Ph) reacted readily at room temp. for 2 h to give **5a,c** in 93 and 97% yields, whilst the reaction of **2** (R^1 = c-Hex, E = CO_2Me) (run 11) was slow

enough at the cyclization step (3 → 5) to obtain 3b (48%) along with 5b (40%) even after 30 h at 80° C. It is now clear that compounds 3 are the key intermediates for the processes. In the presence of silica gel at 80 °C, the separated 3b was quantitatively converted to 5b within a few hours. It is significant that the cyclization step (3 → 5) was effectively accelerated by silica gel (see also runs 13 and 15-18). Treatment of 2 (R^1 = Ph) with butylamine afforded 5e (54%) and 7e (32%), whereas the reaction of 2 (R^1 = c-Hex) with the amine yielded 7f (98%) only. The selectivity in the latter results can be ascribed mainly to the large difference in cyclization rates due to the steric hindrance around the NHHex-c (R^1) and NHBu-n (R^2) groups. Indeed, this assumption is supported by the fact that the same products 7g(= 5h) are obtained exclusively in both reactions (Runs 16 and 17) which involve equilibrium between the configurationally flexible guanidines 3g

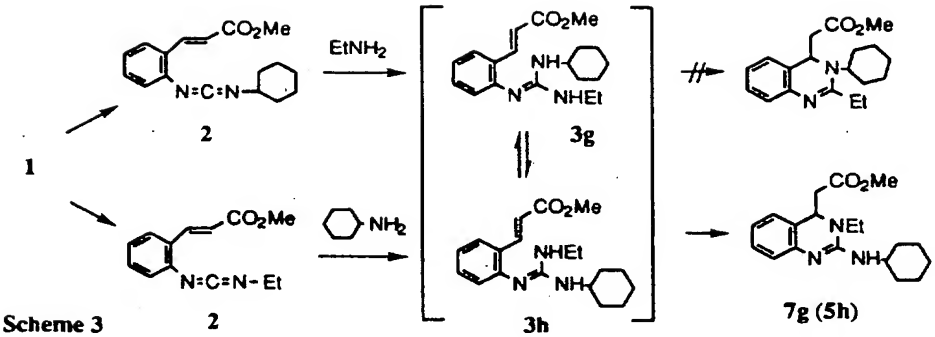


Scheme 2 *Reagents and solvents*:
i, R^1NCO in benzene; ii, R^2XH in MeOH (runs 1-9), benzene (runs 10-17) or toluene (run 18)

Table 1 Reaction of Carbodiimides 2 with Nucleophiles

Run	E	R^1	R^2	X	Reaction conditions	Product (Yield, %)
1	CO_2Me	Ph	Me	O	reflux / 3h	4a (62)
2	CO_2Me	p-Tol	Me	O	reflux / 3h	4b (72)
3	CO_2Me	c-Hex	Me	O	reflux / 40h	4c (78)
4	CO_2Me	Me	Me	O	reflux / 2h	4d (62)
5	CN	Ph	Me	O	reflux / 5h	4e (69)
6	CN	Ph	Me	O	r.t. / 5h / MeONa	4e (68)
7	CN	p-Tol	Me	O	r.t. / 3h / MeONa	4f (75)
8	CN	c-Hex	Me	O	r.t. / 72h / MeONa	4g (76)
9	CN	Me	Me	O	r.t. / 6h / MeONa	4h (98)
10	CO_2Me	Ph	$(CH_2)_5N$		r.t. / 2h	5a (93)
11	CO_2Me	c-Hex	$(CH_2)_5N$		reflux / 30h	3b (48) + 5b (40)
12	CN	Ph	$(CH_2)_5N$		r.t. / 2h	5c (97)
13	CN	c-Hex	$(CH_2)_5N$		r.t. / 0.5h → reflux / 5h[a]	5d (97)
14	CO_2Me	Ph	n-Bu	NH	r.t. / 0.5h → reflux / 2h	5e (54) + 7e (32)
15	CO_2Me	c-Hex	n-Bu	NH	r.t. / 2h → reflux / 2h[a]	7f (98)
16	CO_2Me	c-Hex	Et	NH	r.t. / 14h → r.t. / 2h[a]	7g (=5h) (96)
17	CO_2Me	Et	c-Hex	NH	r.t. / 2.5h → r.t. / 2h[a]	5h (=7g) (98)
18	CO_2Me	Ph	p-Tol	S	reflux / 1h → r.t. / 1d[a]	6a (70)

[a] Silica gel (ca. 1g) was added after completion of the initial addition step (2 → 3).



Scheme 3

and **3h** as depicted in Scheme 3. Finally, a thiol was also found to play a role in the tandem carbodiimide-mediated nucleophilic addition-intramolecular hetero conjugate addition annulation to give **6a**.

In summary, the functionalized dihydroquinazoline compounds could readily and efficiently be synthesized via the tandem additions strategy. Further study on this subject is in progress in our laboratory.

Typical Procedure (Table 1, Run 11)

To a benzene solution (15 cm^3) of carbodiimide **2** (0.70 mmol, 198 mg) was dropwise added a benzene solution (15 cm^3) of piperidine (0.75 mmol) at room temperature with stirring under an atmosphere of argon. After additional stirring at r.t., the reaction mixture was then heated under reflux for 30 h. Evaporation of the solvent and column chromatography of the residue gave guanidine **3b** (48%) as an oil and dihydroquinazoline **5b** (40%) as pale brownish crystals (recrystallized from CH_2Cl_2-hexane).

3b: δ_H 0.86-1.30 (m, 8H), 1.50-1.64 (m, 7H), 1.83-1.88 (m, 2H), 3.19 (m, 5H), 3.77 (s, 3H), 6.43 (d, 1H, J 16.17 Hz), 6.79 (dd, 1H, J 7.26 and 0.99), 6.93 (ddd, 1H, J 7.26, 7.26 and 0.66 Hz), 7.24 (ddd, 1H, J 7.91, 7.26 and 1.32 Hz) and 7.52 (dd, 1H, J 7.91 and 1.32 Hz).

5b: mp. 128-129 °C; MS m/z 369 (M^+, 40%) and 214 (100%); δ_H 1.06-1.32 (m, H), 1.54-1.89 (m, H), 2.34 (dd, 1H, J 14.18 and 5.27 Hz), 2.51 (dd, 1H, J 14.18 and 9.57 Hz), 3.17-3.71 (m, H), 3.65 (s, 3H), 4.70 (dd, 1H, J 9.57 and 5.27 Hz), 6.93 (ddd, 1H, J 7.26, 7.26 and 1.32 Hz), 7.01 (dd, 1H, J 7.26 and 1.32 Hz); 7.08 (dd, 1H, J 7.26 and 1.32 Hz) and 7.16 (ddd, 1H, J 7.26, 7.26 and 1.32 Hz).

4a: oil; m/z 310 (M+, 9%), 237 (100%); M, m/z 310.1314. $C_{18}H_{18}N_2O_3$ requires M, 310.1318; IR 1740 cm^{-1}; δ_H 2.70 (dd, 1H, J 14.84 and 7.59 Hz), 2.80 (dd, 1H, J 14.84 and 5.28 Hz), 3.52 (s, 3H), 3.87 (s, 3H), 5.26 (dd, 1H, J 7.59 and 5.28 Hz) and 6.97-7.39 (m, 9H); ^{13}C NMR δ 40.63 (CH_2), 51.70 (CH_3), 54.34 (CH_3), 60.07 (CH), 123.23 (CH)-170.69 (CO).

6a: oil; MS m/z 402 (M^+, 15); HRMS m/z 402.1409. $C_{24}H_{22}N_2O_2S$ requires M, 402.1404; IR 1732 cm^{-1}; δ_H 2.31 (s, 3H), 2.75 (d, 2H, J 6.93 Hz), 3.61 (s, 3H), 5.07 (t, 1H, J 6.93 Hz) and 6.95-7.28 (m, 13H).

7f: oil; MS m/z 357 (M^+, 13); HRMS m/z 357.2415. $C_{21}H_{13}N_3O_2$ requires M, 357.24183; IR 3424 and 1726 cm^{-1}; δ_H 0.870 (t, 3H, J 7.26 Hz), 1.06-1.46 (m, 7H), 1.53 (ddt, 2H, J 7.26, 7.26 and 7.26 Hz), 1.59-1.76 (m, 3H), 2.04-2.08 (m, 3H), 2.44 (dd, 1H, J 14.85 and 6.59 Hz), 2.67 (dd, 1H, J 14.85 and 7.26 Hz), 3.14 (dt, 1H, J 14.52 and 7.26 Hz), 3.39 (dt, 1H, J 14.52 and 7.26 Hz), 3.64 (s, 3H), 4.82 (br. s, 1H), 4.66 (dd, 1H, J 7.26 and 6.59 Hz) and 6.83-7.19 (m, 4H).

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